CHROMOSOMES
Inventor(s): Kazuma TOMIZUKA et
al.
DOCKET NO.: 081356/0158

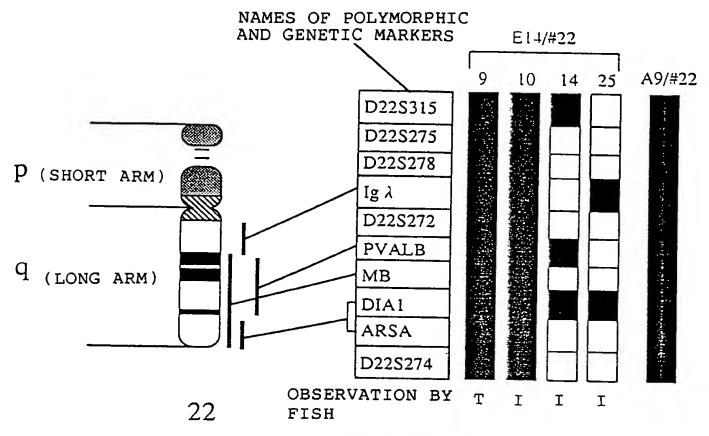
I: INDEPENDENT

T: TRANSLOCATED

CHROMOSOMES
Inventor(s): Kazuma TOMIZUKA et

al.

DOCKET NO.: 081356/0158



T: TRANSLOCATED I: IN

I: INDEPENDENT

FIG. 2



Inventor(s): Kazuma TOMIZUKA et al.

DOCKET NO.: 081356/0158

CHIMERIC MICE (K22-)
C 12 11 10 9 8 7 6

23kb9.4kb6.6kb-

CHIMERISM

6 + 7 + 8 ++ 9 - 10 + 11 + 12 +

FIG. 3

ventor(s): Kazuma TOMIZUKA et al.
DOCKET NO.: 081356/0158

B: brain
L: liver
SM: skeletal muscle
H: heart
Sp: spleen
Th: thymus
Ov: ovary
K: kidney

2

Sp Th Ov

I

SM

 \mathbf{m}

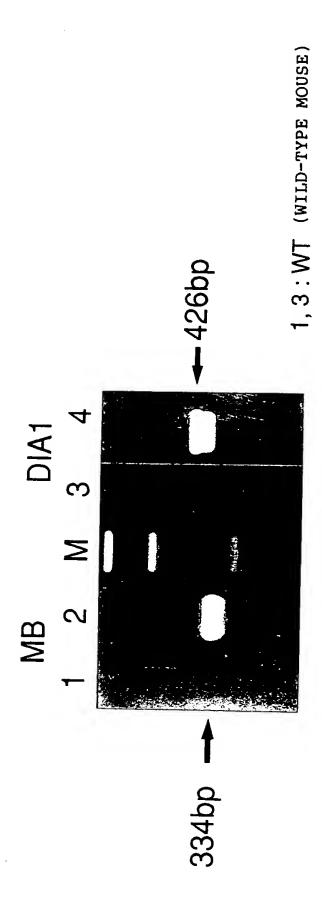
NC : NEGATIVE CONTROL pc : POSITIVE CONTROL

DIA1: HUMAN CYTOCHROME D5 REDUCTASE

4/71

Inventor(s): Kazuma TOMIZUKA al. DOCKET NO.: 081356/0158

2, 4: K22-7



MB : HUMAN MYOGLOBIN

DIA1: HUMAN CYTOCHROME D5 REDUCTASE

al. DOCKET NO.: 081356/0158

L: LIVER
Sp: SPLEEN
K: KIDNEY
Ov: OVARY
SM: SKELETAL MUSCLE
M: MOLECULAR WEIGHT MARKER B:BRAIN H:HEART Th:THYMUS

≥ SM ò \mathbf{X} Sp エ Θ

MB; HUMAN MYOGLOBIN

DIA1 : HUMAN CYTOCHROME D5 REDUCTASE

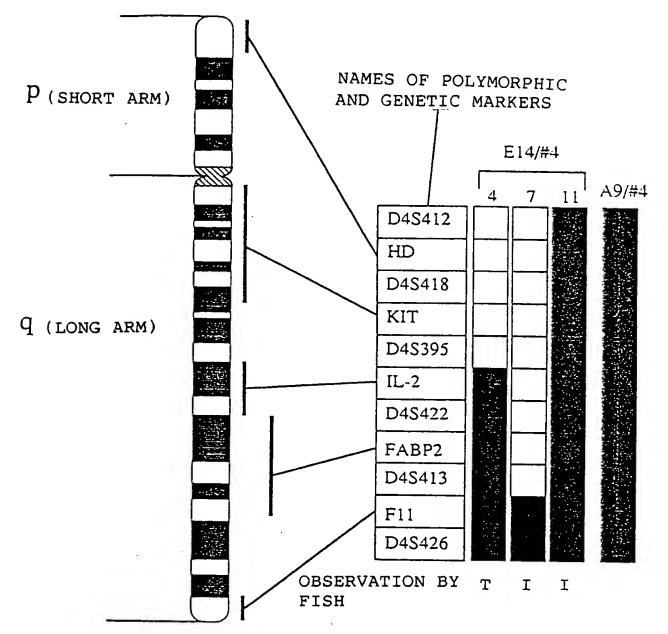
9

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Inventor(s): Kazuma TOMIZUKA et

al.

DOCKET NO.: 081356/0158



T: TRANSLOCATED I: INDEPENDENT

4

FIG. 7

The state of the s



Inventor(s): Kazuma TOMIZUKA

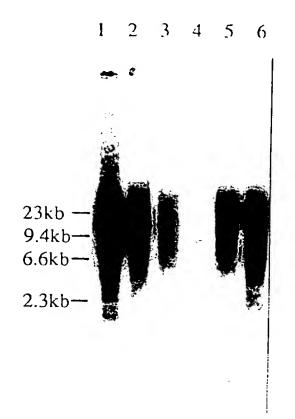


FIG. 8



CHROMOSOMES
Inventor(s): Kazuma TOMIZUKA e
al.
DOCKET NO.: 081356/0158

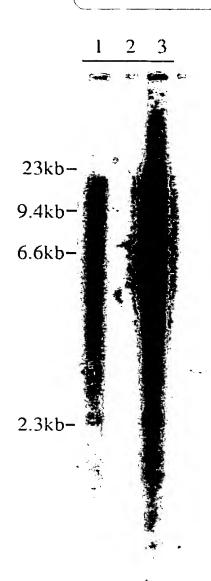


FIG. 9

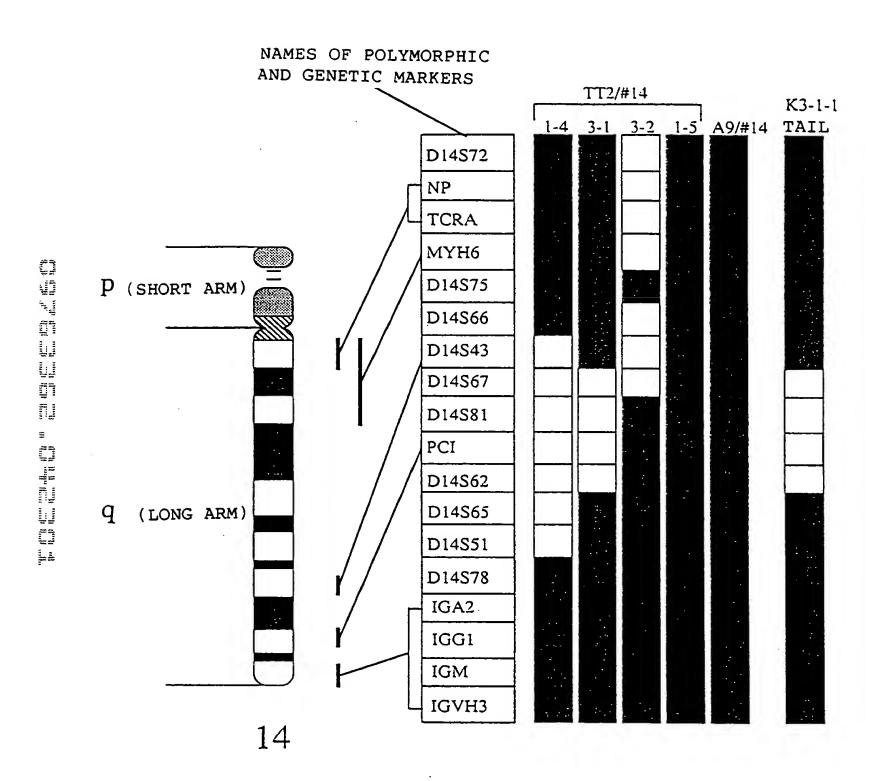


FIG. 10

Inventor(s): Kazuma TOMIZUKA e al.

DOCKET NO.: 081356/0158

NC: NEGATIVE CONTROL
M: MOLECULAR WEIGHT MARKER

pc : POSITIVE CONTROL

B: BRAIN
K: KIDNEY
Sp:SPLEEN
H: HEART
L: LIVER
Th: THYMUS

20 bc 工 Sp മ

|gM| : HUMAN IMMUNOGLOBULIN μ CHAIN

Inventor(s): Kazuma TOMIZUKA et al.

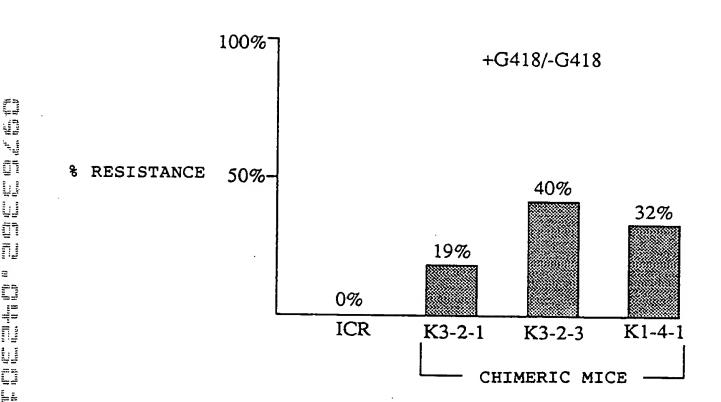
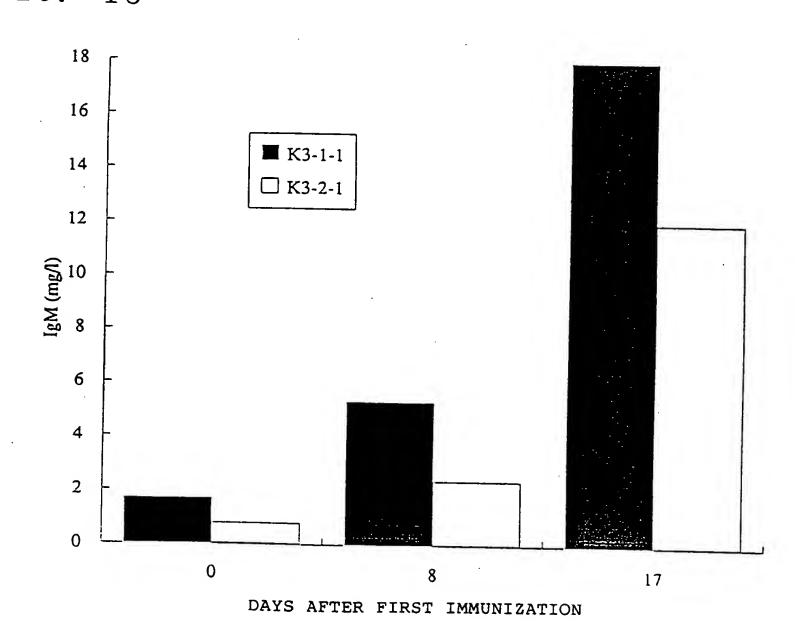


FIG. 12

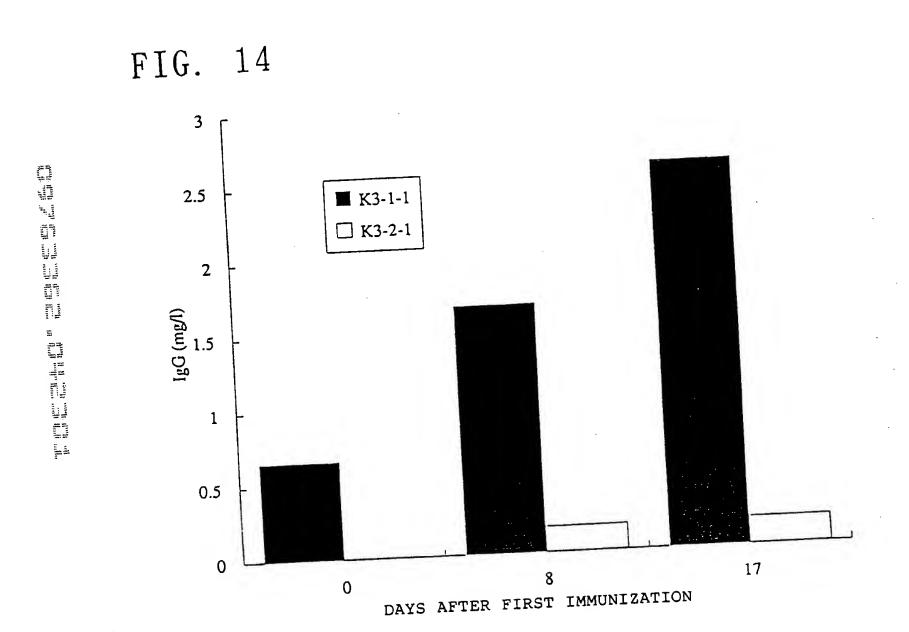
FIG. 13



09/763362

Inventor(s): Kazuma TOMIZUKA e

al.



Inventor(s): Kazuma TOMIZUKA et

al. DOCKET NO.: 081356/0158

FIG. 15 3.00 - PURIFIED HUMAN IGM 2.50 - H4B7 CULTURE SUPERNATANT 2.00 ABSORBANCE 1.50 1.00 0.50 0.00 2 8 4 16 32 64 128 256

DILUTION

CHROMOSOMES Inventor(s): Kazuma TOMIZUKA et

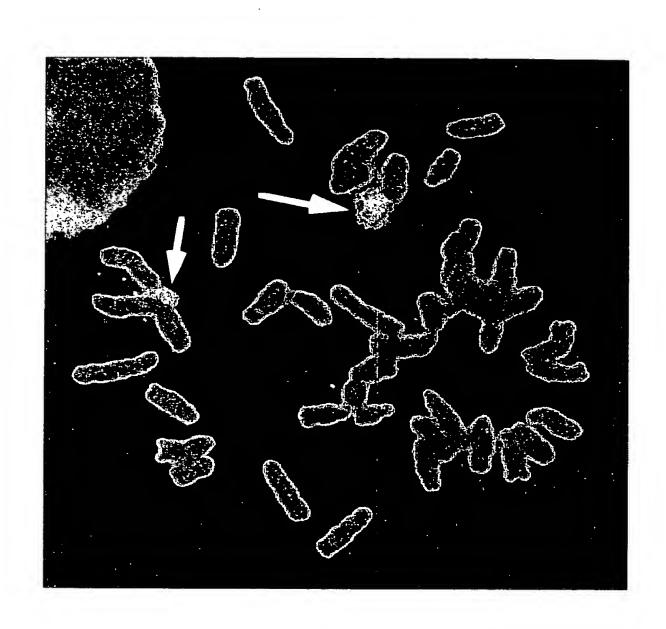
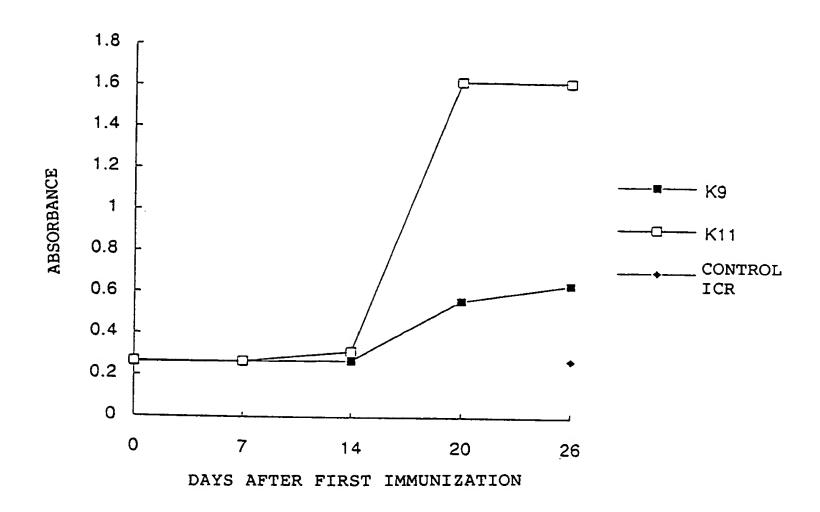


FIG. 16

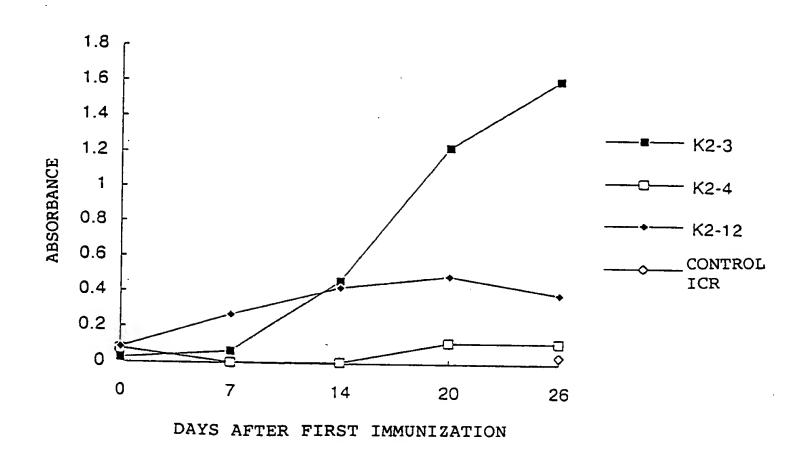
Inventor(s): Kazuma TOMIZUKA

FIG. 17



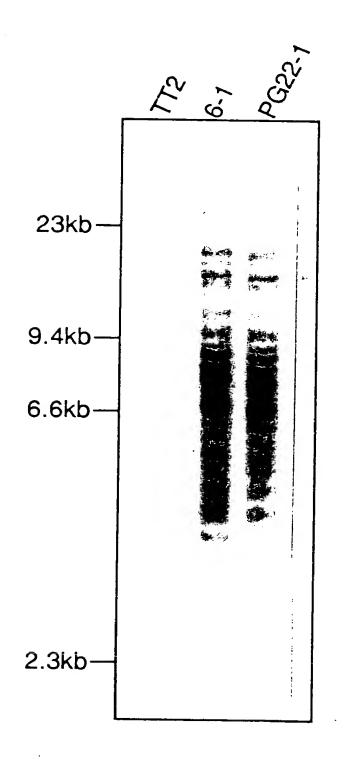
Inventor(s): Kazuma TOMIZUKA e

FIG. 18



Inventor(s): Kazuma TOMIZUKA al.

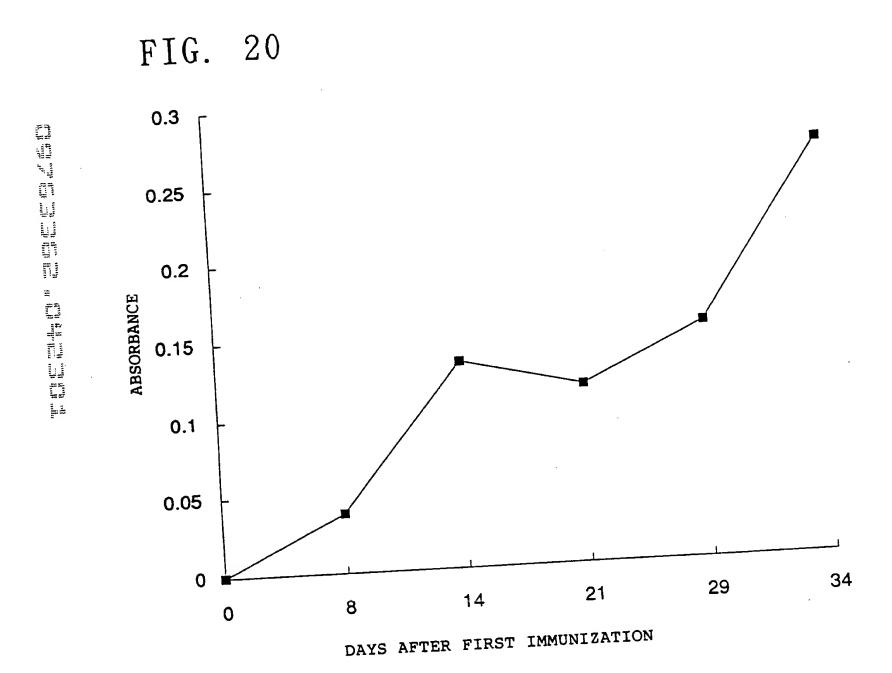
FIG. 19



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Inventor(s): Kazuma TOMIZUKA et

al.

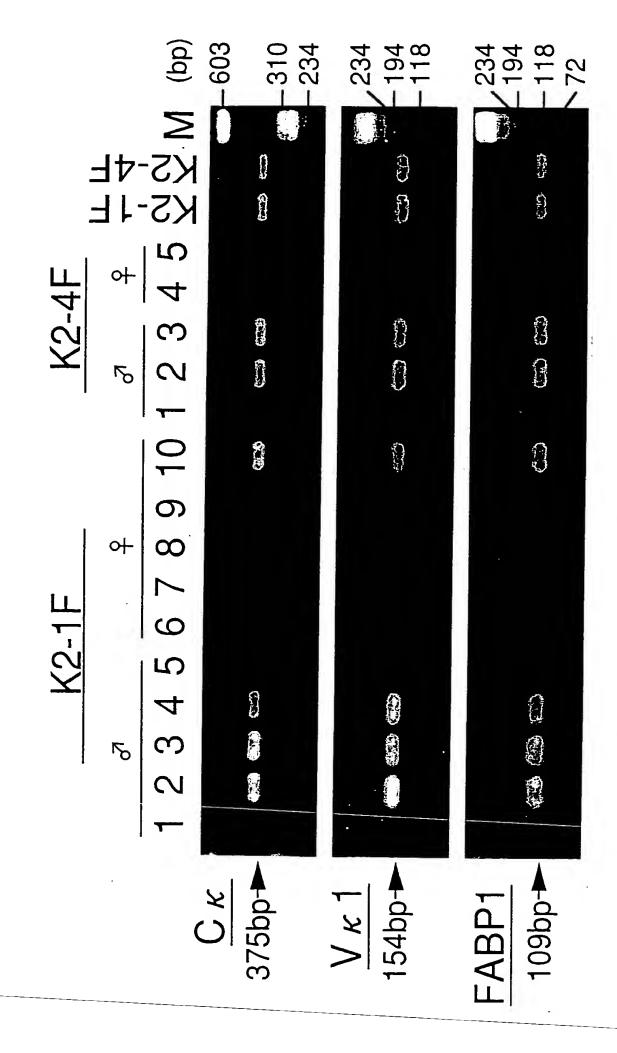


CHROMOSOMES Inventor(s): Kazuma TOMIZUKA et al.

DOCKET NO.: 081356/0158

FIG. 21

the first thin than the first the track of the first than the first that the first that the



9%

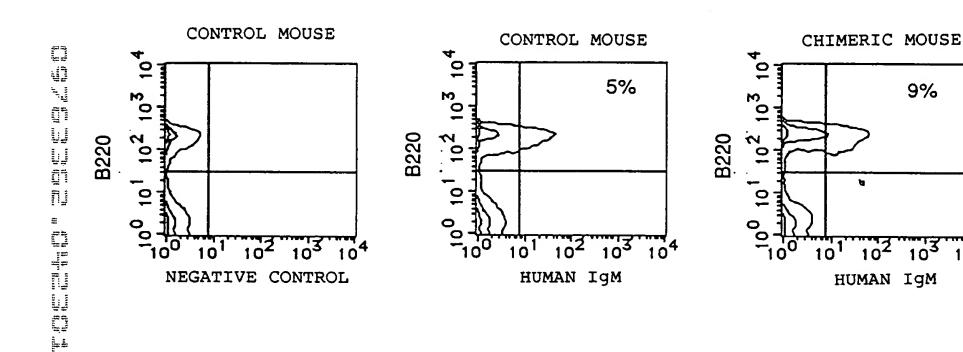


FIG. 22

CHROMOSOMES 09/763362

FIG. 23

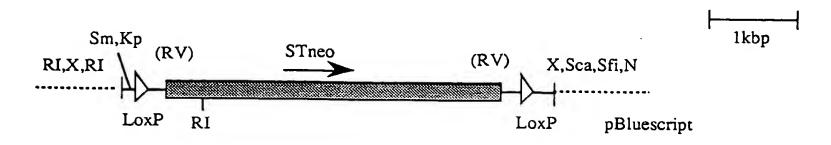


FIG. 24

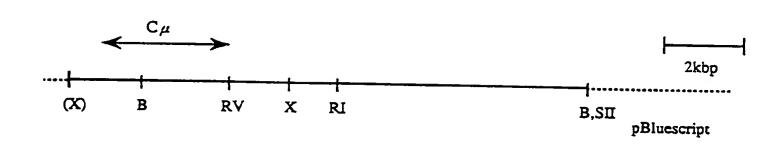
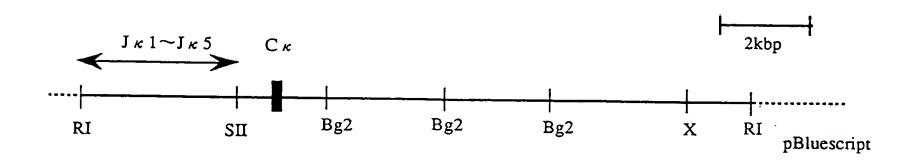


FIG. 25



CHROMOSOMES
Inventor(s): Kazuma TOMIZUKA et

DOCKET NO.: 081356/0158

FIG. 26

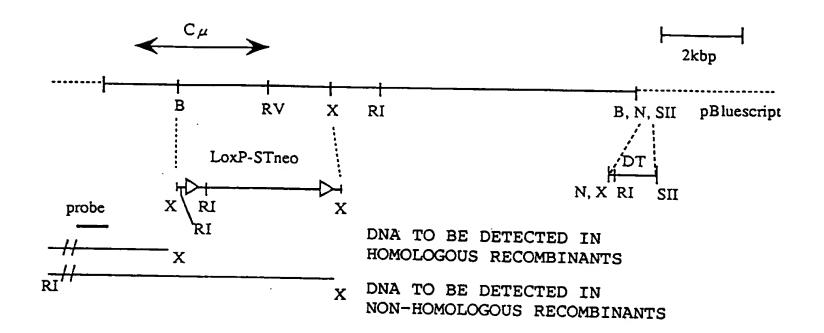
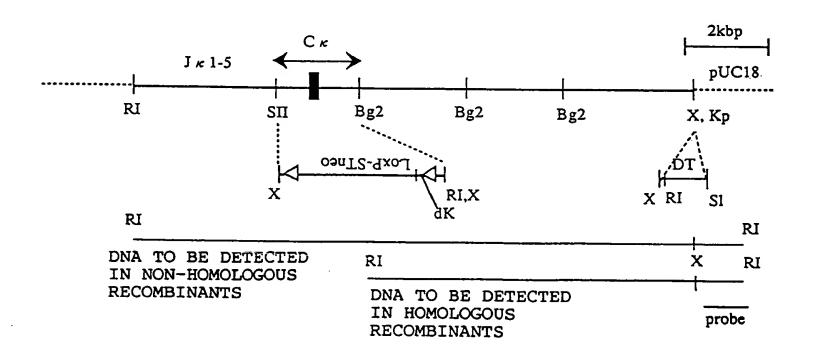
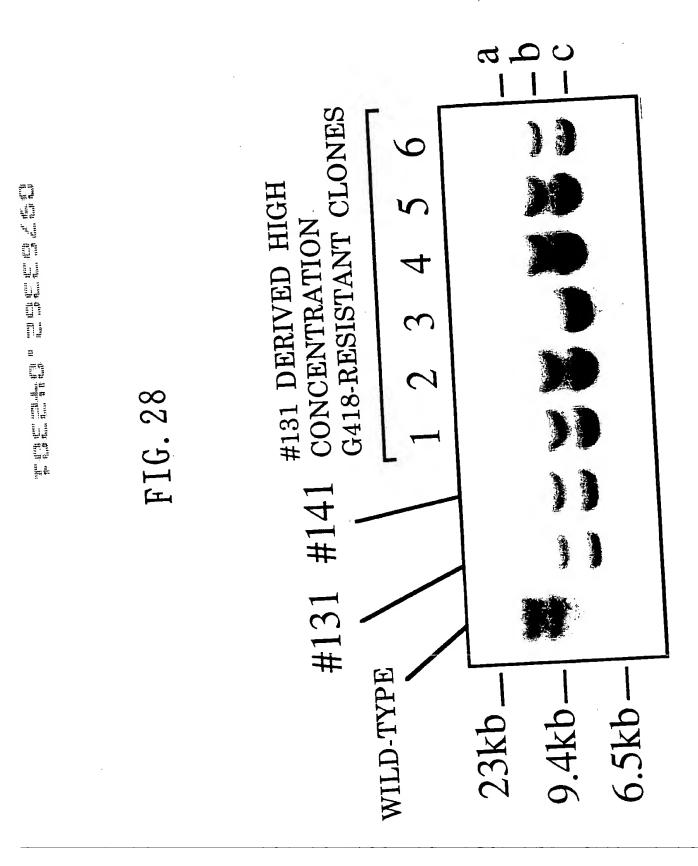


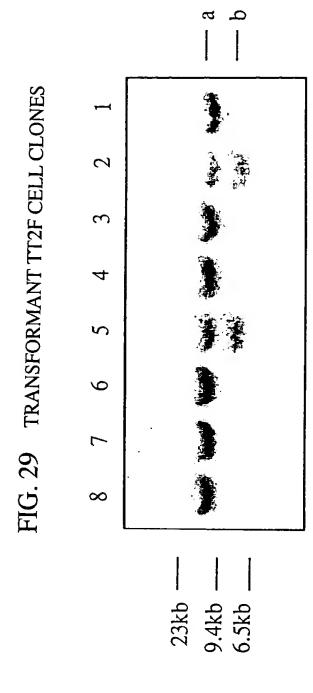
FIG. 27







Inventor(s): Kazuma TOMIZUKA e



Inventor(s): Kazuma TOMIZUKA et al.

DOCKET NO.: 081356/0158

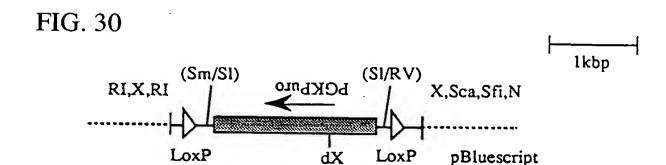
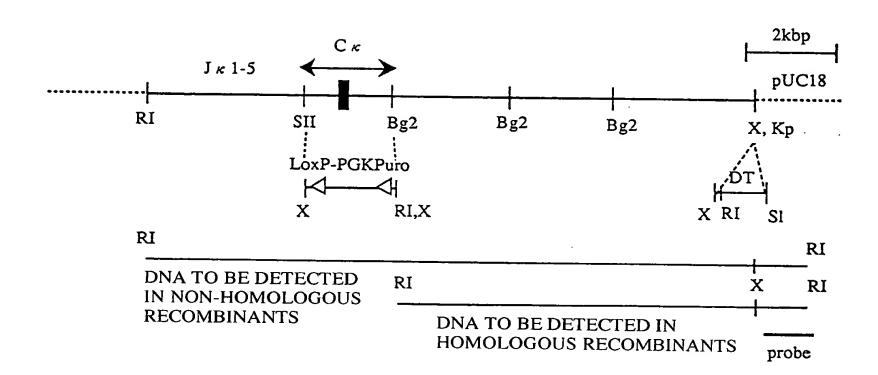


FIG. 31

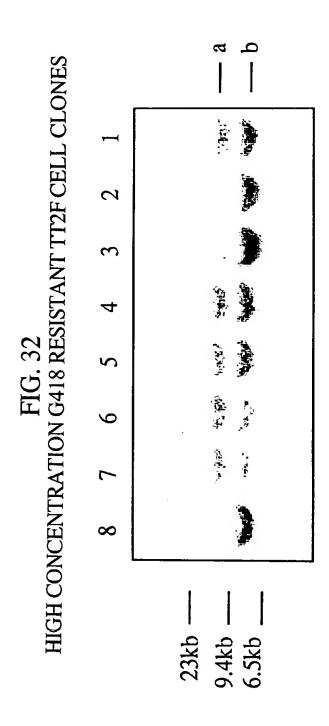


RESTRICTION ENZYMES:

Kp: KpnI, B: BamHI, Bg2:Bgl2, RI: EcoRI, RV: EcoRV, N: Not, Sl: SalI, Sca: ScaI, Sfi: SfiI, Sm: Sma, X: XhoI, (X): XhoI RESTRICTION SITE FROM λ VECTOR dK: KpnI RESTRICTION SITE DELETED, dX: XhoI RESTRICTION SITE DELETED (Sm/Sl): LIGATED TO Smal RESTRICTION SITE AFTER Sall BLUNTING (SI/RV): LIGATED TO EcoRV RESTRICTION SITE AFTER Sall BLUNTING DOTTÉD PORTION: pBluescript SKII(+) OR pUC18 PLASMID DNA

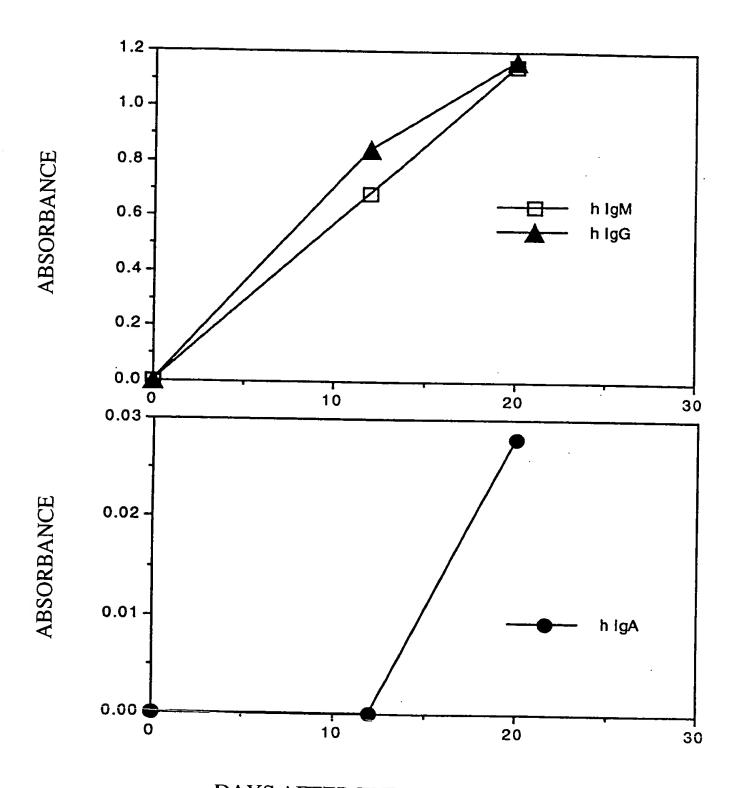
Inventor(s): Kazuma TOMIZUKA et al.

DOCKET NO.: 081356/0158



Inventor(s): Kazuma TOMIZUKA et al.

FIG. 33



DAYS AFTER THE FIRST IMMUNIZATION

09/763362

CHROMOSOMES
Inventor(s): Kazuma TOMIZUKA et

al.

DOCKET NO.: 081356/0158

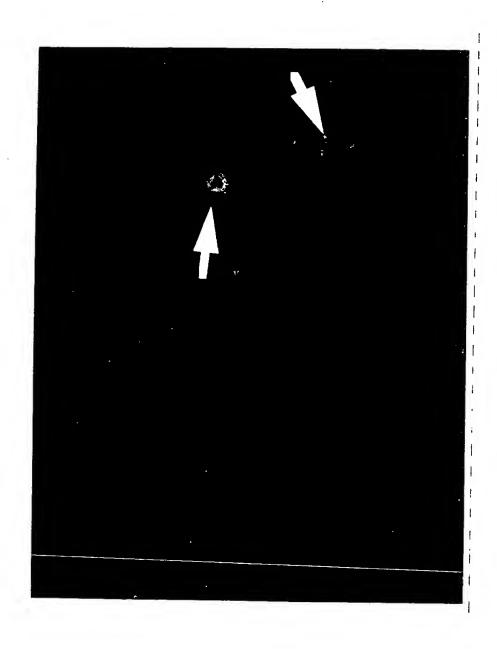
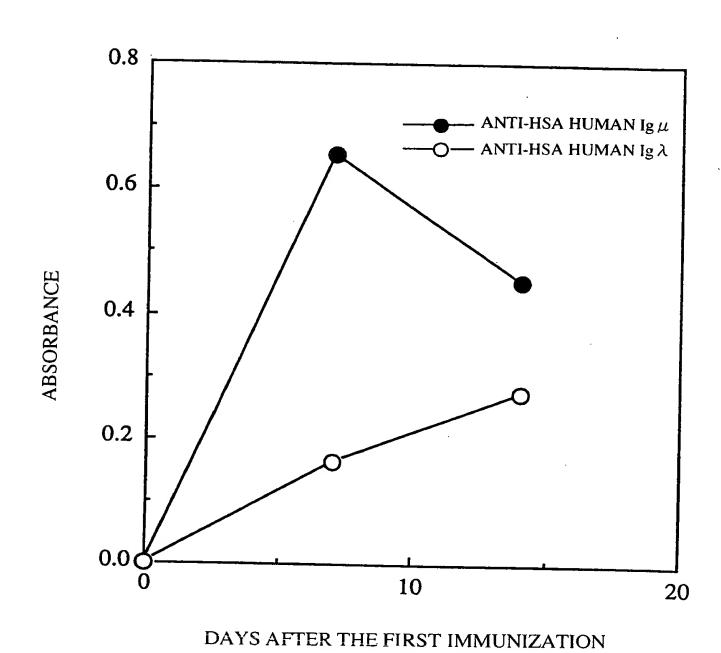


FIG. 34

Inventor(s): Kazuma TOMIZUKA et al.

DOCKET NO.: 081356/0158

FIG. 35



The grap grave will also been the first street from the grave grav

09/763362

Title. METHOD FOR MODIFY IN 9 CHROMOSOMES
Inventor(s): Kazuma TOMIZUKA et

al.

DOCKET NO.: 081356/0158



al.
DOCKET NO.: 081356/0158

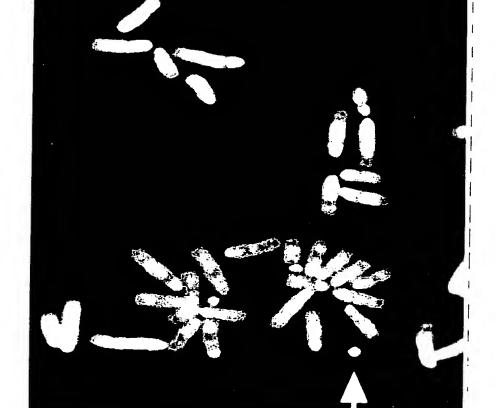


FIG. 37

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al.

DOCKET NO.: 081356/0158

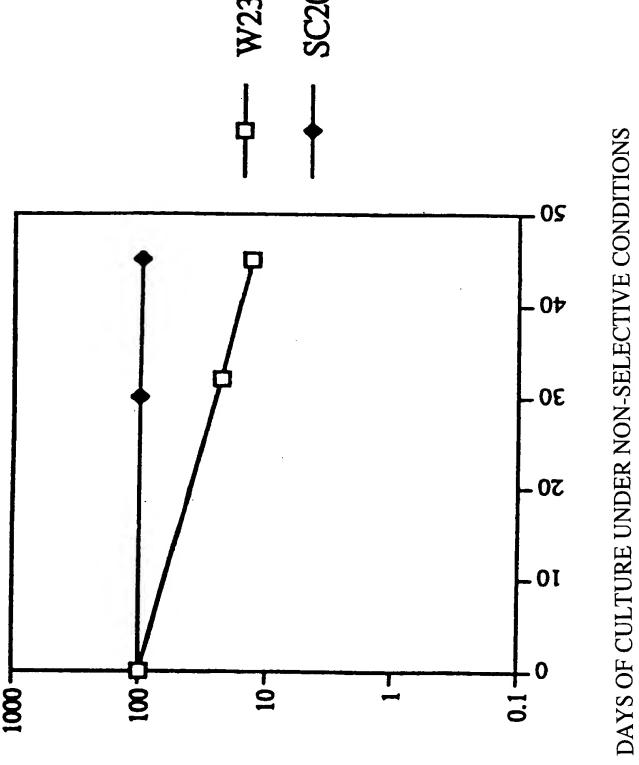


FIG. 38

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To the first than the it that

IN TT2F CELLS (%)
RATIO OF CHROMOSOME RETENTION

and find the third fine the time that find

The third their think it is the

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			Σ	<u>_</u>	4	23		27		12	
			SPERM	+		11 (32%)		14 (34%)		13 (52%)	
	S		IST MEIOSIS 2ND MEIOSIS	_		 -		2		က	
	TESTIS			+		15 (94%)		9 (53%)		13 (81%)	
			IST MEIOSIS			0		0		0	
				+		15 (100%)		16 (100%)		15 (100%)	
	BONE MARROW		l			30		28		25	
	BONEM		+			1 (3%)		21 (43%)	5 (17%)		
	VER		I			1		0		Н	
	LIN		+			30 (97%)		30 (100%)		31 (97%)	
	SPLEEN		l			42		788		34	
	TdS		+		7	(21%)		12 (30%)	7 (17%)		
	NIN		l			0		0		2	
	BRAIN		+		30	(100%)	30 (100%)		41 (95%)		
					16-5	(F1)		17-8 (F1)	(17-23 (F1)	

RETENTION OF SC20 FRAGMENT IN MICE

CHROMOSOMES
Inventor(s): Kazuma TOMIZUKA
al.

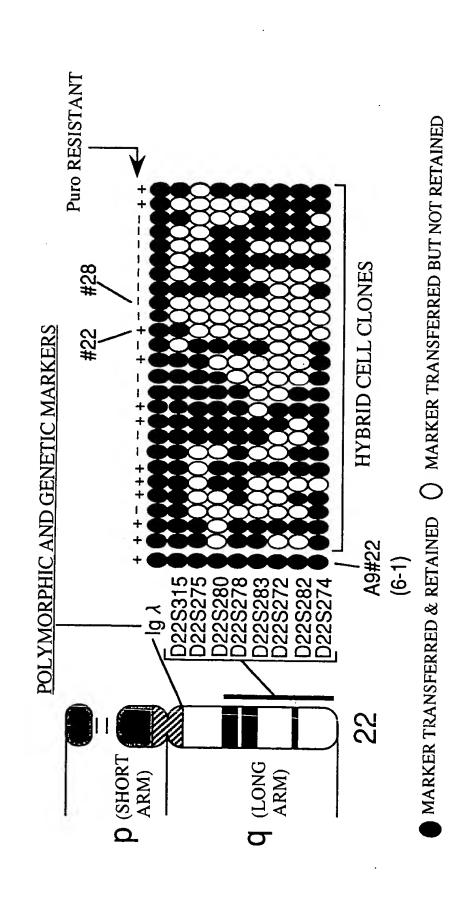
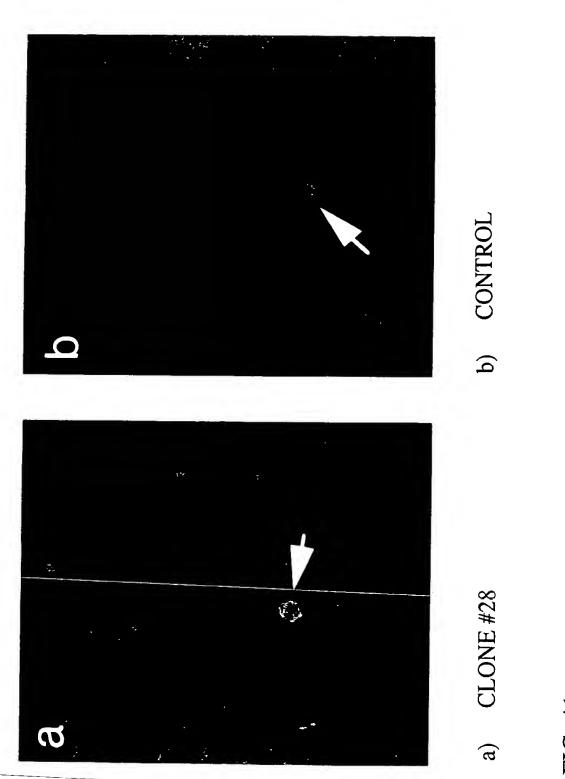


FIG. 4

The State State of the Best State of the Sta



al. DOCKET NO.: 081356/0158

	HK23	HK28	HK29
ANTIBODY HEAVY-CHAIN KNOCKOUT	ОМОН	WILD-TYPE OR HETERO	WILD-TYPE OR HETERO WILD-TYPE OR HETERO
ANTIBODY LIGHT-CHAIN KNOCKOUT	HETERO	WILD-TYPE	HETERO
W23 FRAGMENT	+	+	+
SC20 FRAGMENT	+	+	+
HUMAN μ CHAIN IN SERUM (mg/l)	100	5.9	14
HUMAN κ CHAIN IN SERUM (mg/l)	8.6	8.4	25
HUMAN μ/κ CHAINS IN SERUM (mg/l)	18	0.13	BELOW DETECTION LIMIT

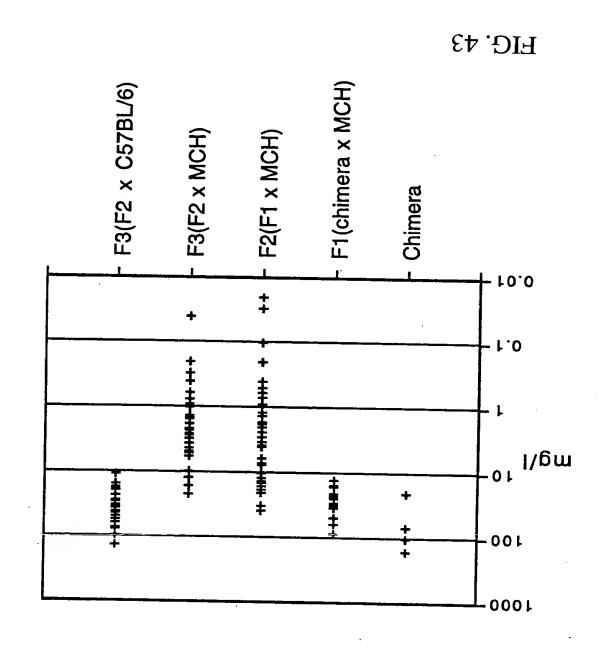
SINCE "ANTIBODY HEAVY-CHAIN KNOCKOUT" IS JUDGED BY THE PRESENCE OR ABSENCE OF THE EXPRESSION OF MOUSE $\,\mu\,$ CHAIN, IT IS IMPOSSIBLE TO DISCRIMINATE HETERO FROM WILD-TYPE.

* "ANTIBODY LIGHT-CHAIN KNOCKOUT" IS JUDGED BY SOUTHERN BLOT ANALYSIS.

FIG 4

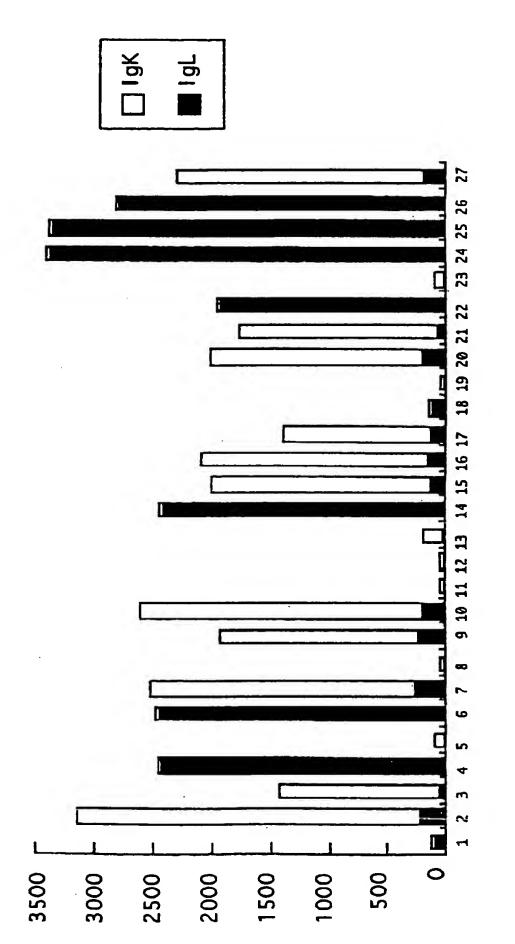
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DOCKEL NO:: 081326/0128 Inventor(s): Kazuma TOMIZUKA et CHBOWOSOWES
Litte: WELHOD FOR MODIFYING



al.

DOCKET NO.: 081356/0158



MOUSE ANTIBODY LIGHT-CHAIN (μ g/ml)

40/71

1 kb (TTAGGG)n RV; Eco RV RI; Eco RI Sp; Spe I N; Not I pBluescript II PGK Puro PGK Puro Eco RI DIGESTION pBluescript SK II (-) RI (TTAGGG)n LIF (RV)

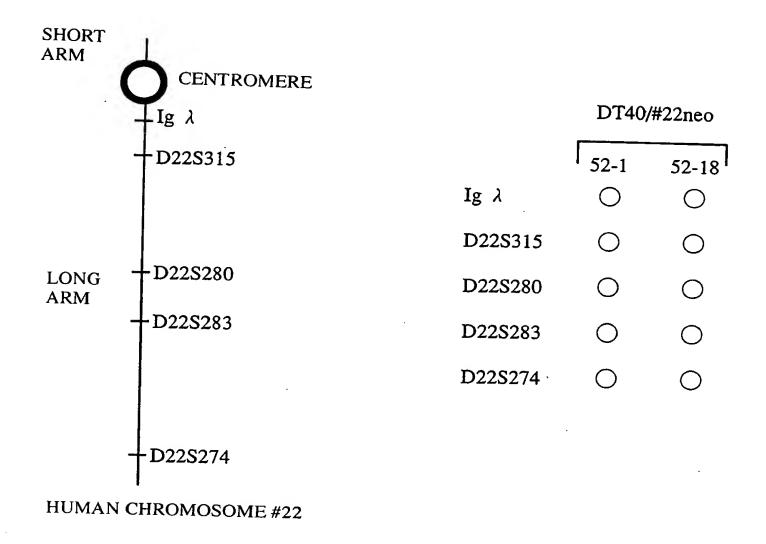
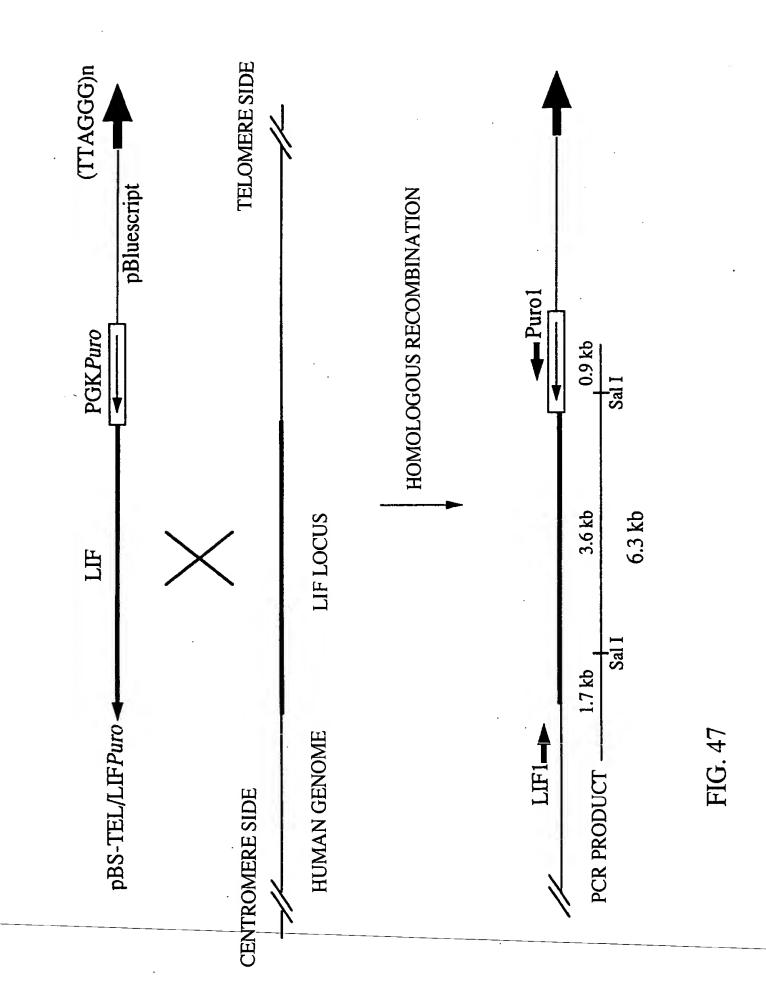


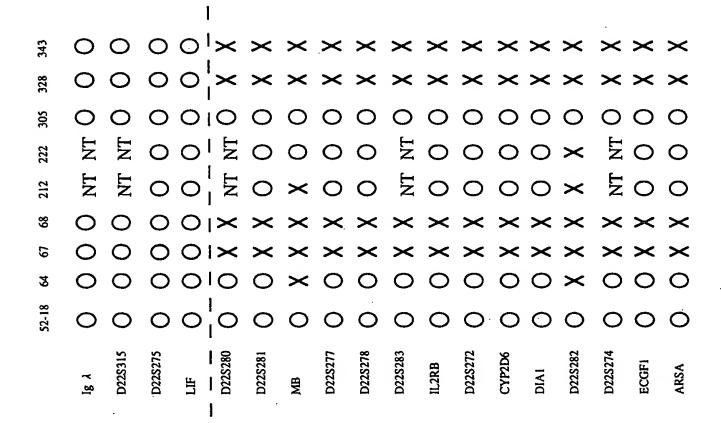
FIG. 46

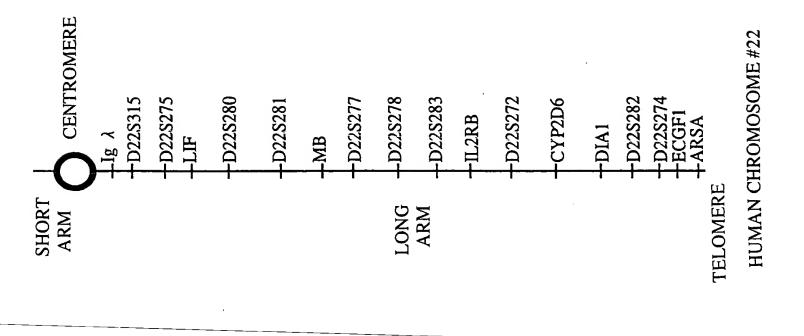
al. DOCKET NO.: 081356/0158

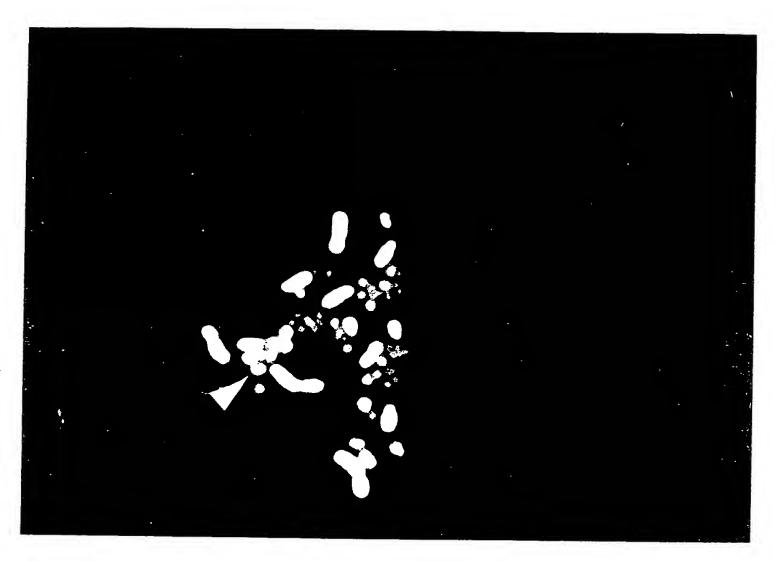


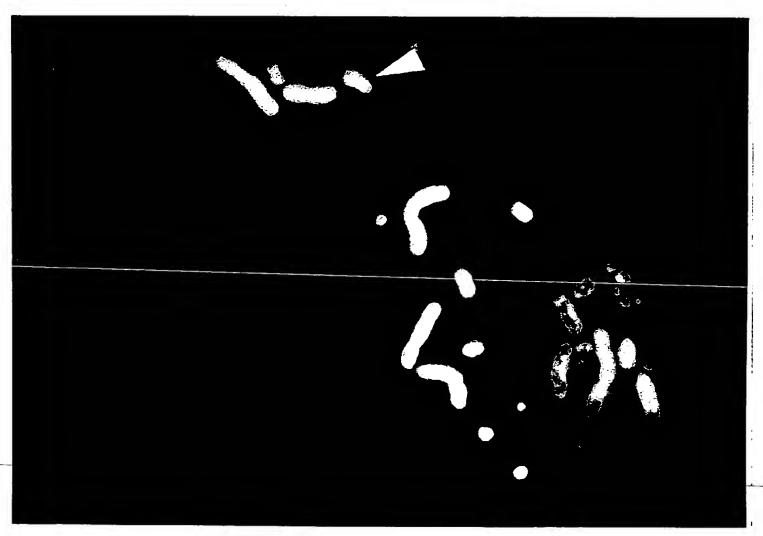
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CHROMOSOMES Inventor(s): Kazuma TOMIZUKA et









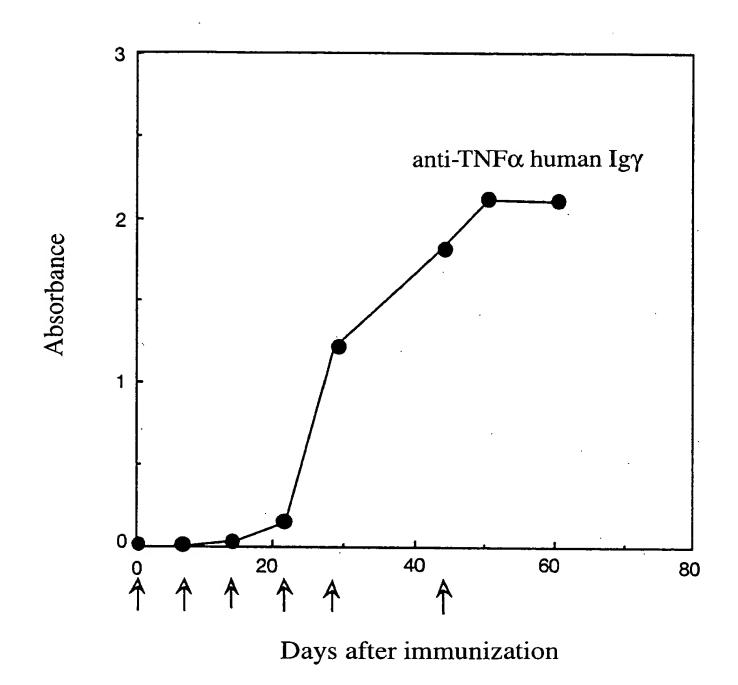


FIG. 50

DOCKET NO.: 081356/0158

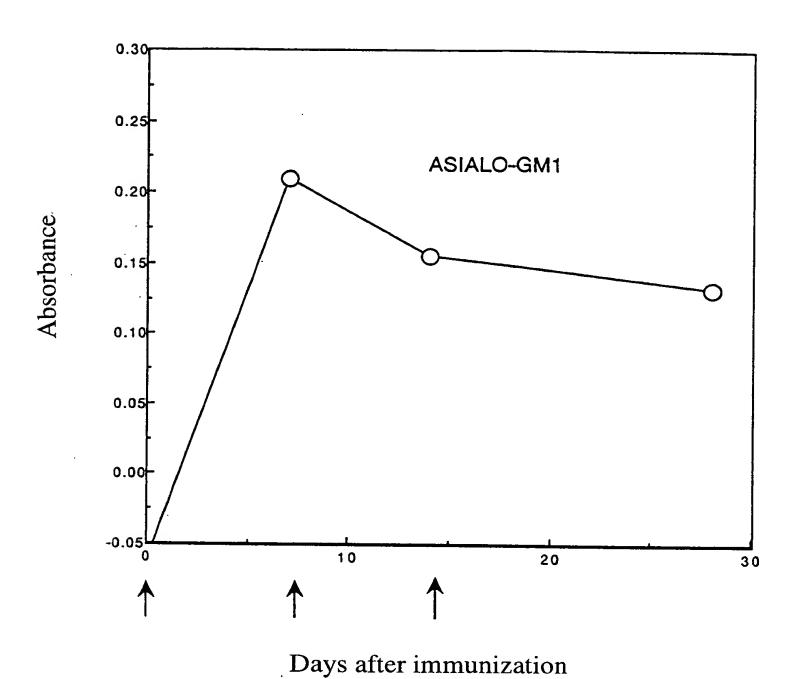


FIG. 51

DOCKET NO.: 081356/0158

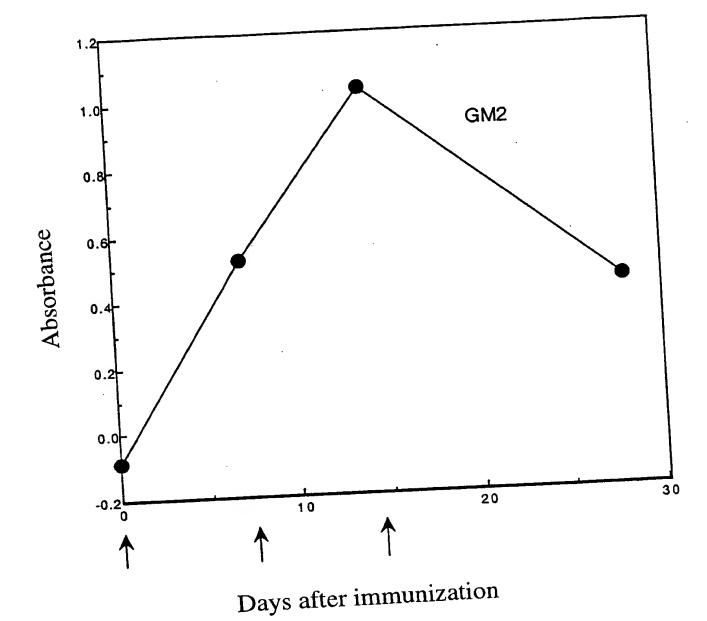
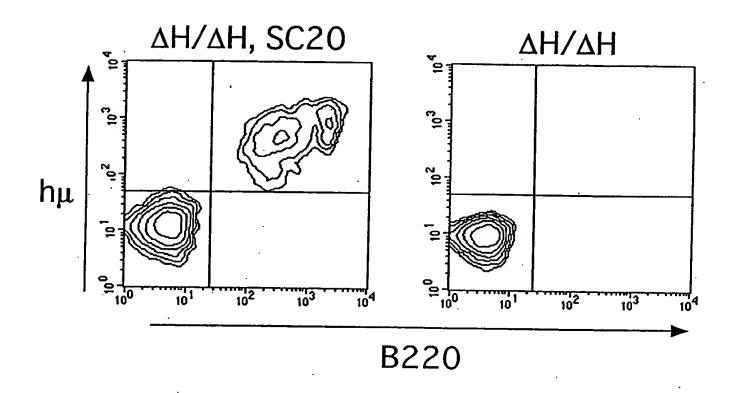


FIG. 52

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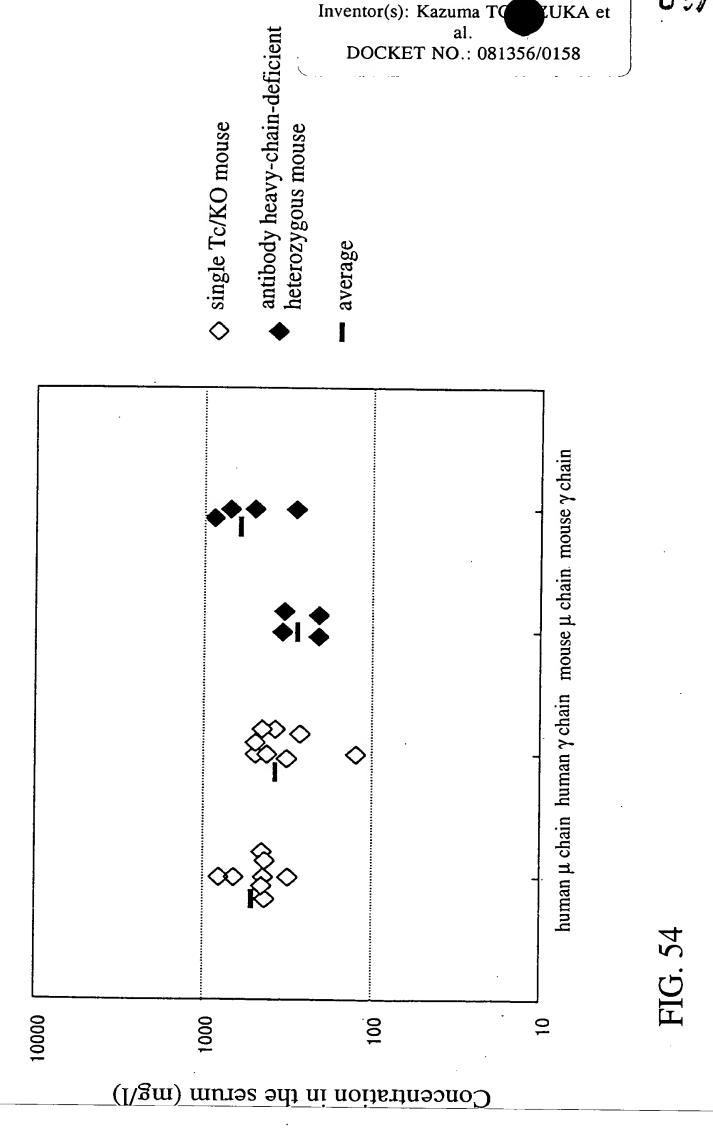
DOCKET NO.: 081356/0158



 Δ H/ Δ H, SC20: Single Tc/KO mouse

 Δ H/ Δ H: antibody heavy-chain KO mouse

FIG. 53



Title: METHOD FOR MODIFYING

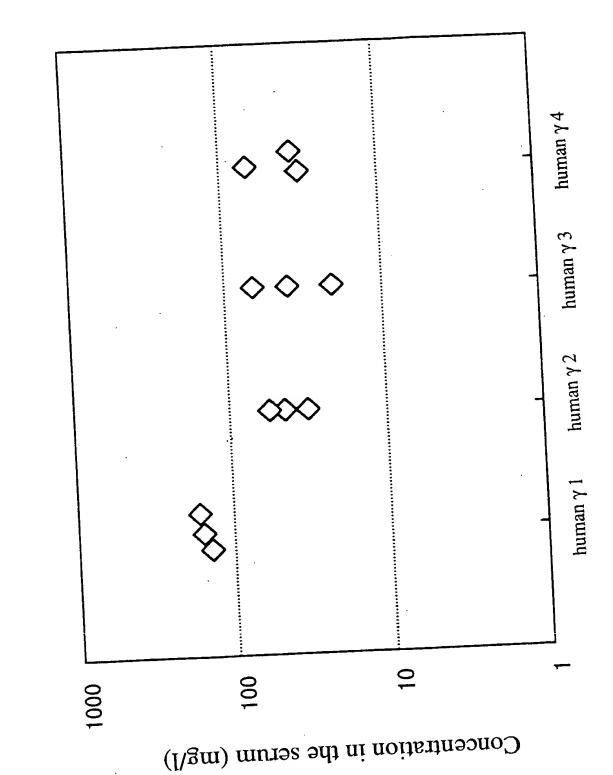
CHROMOSOMES

ventor(s): Kazuma TOMIZUKA et

al. DOCKET NO.: 081356/0158

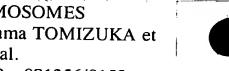


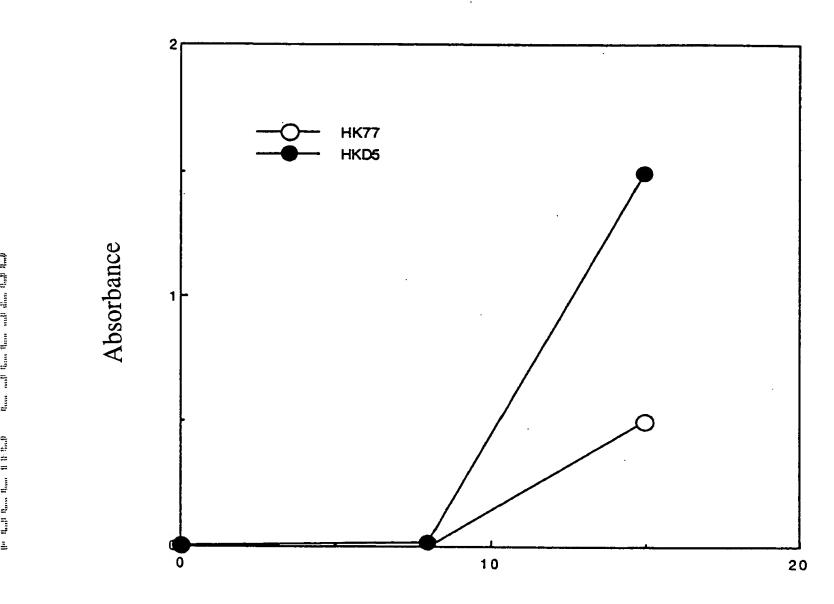
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The first time and the first time in the first time that the fact that the

FIG.





Days after immunization

FIG. 56

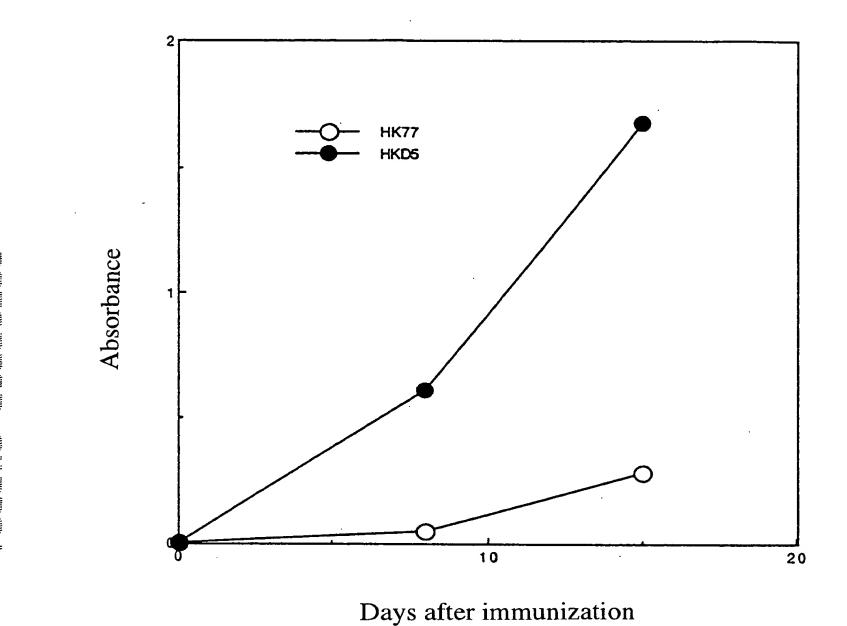
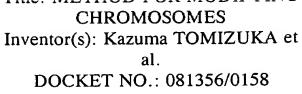
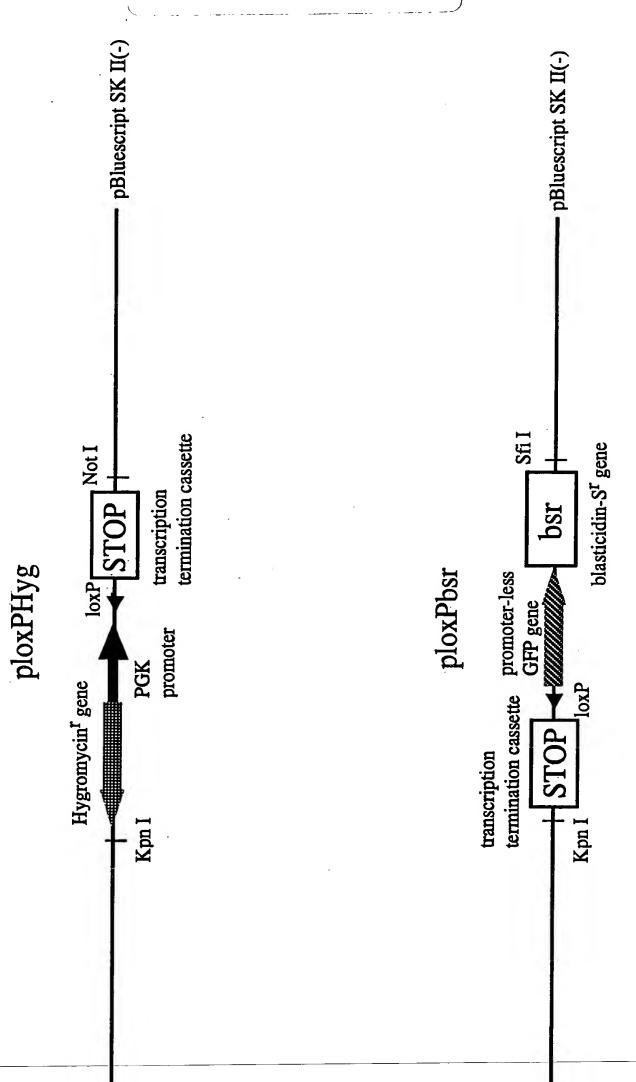


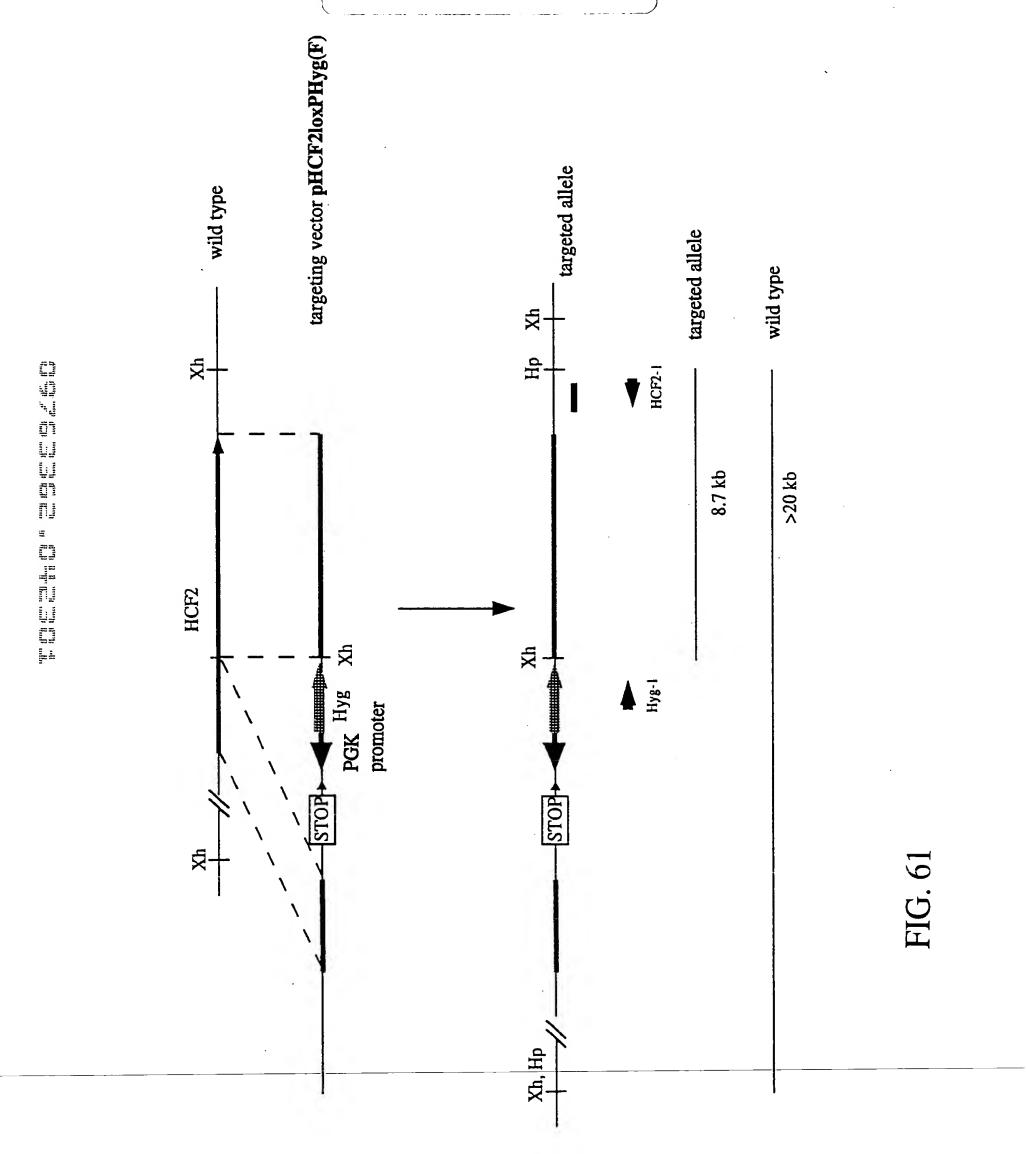
FIG. 57

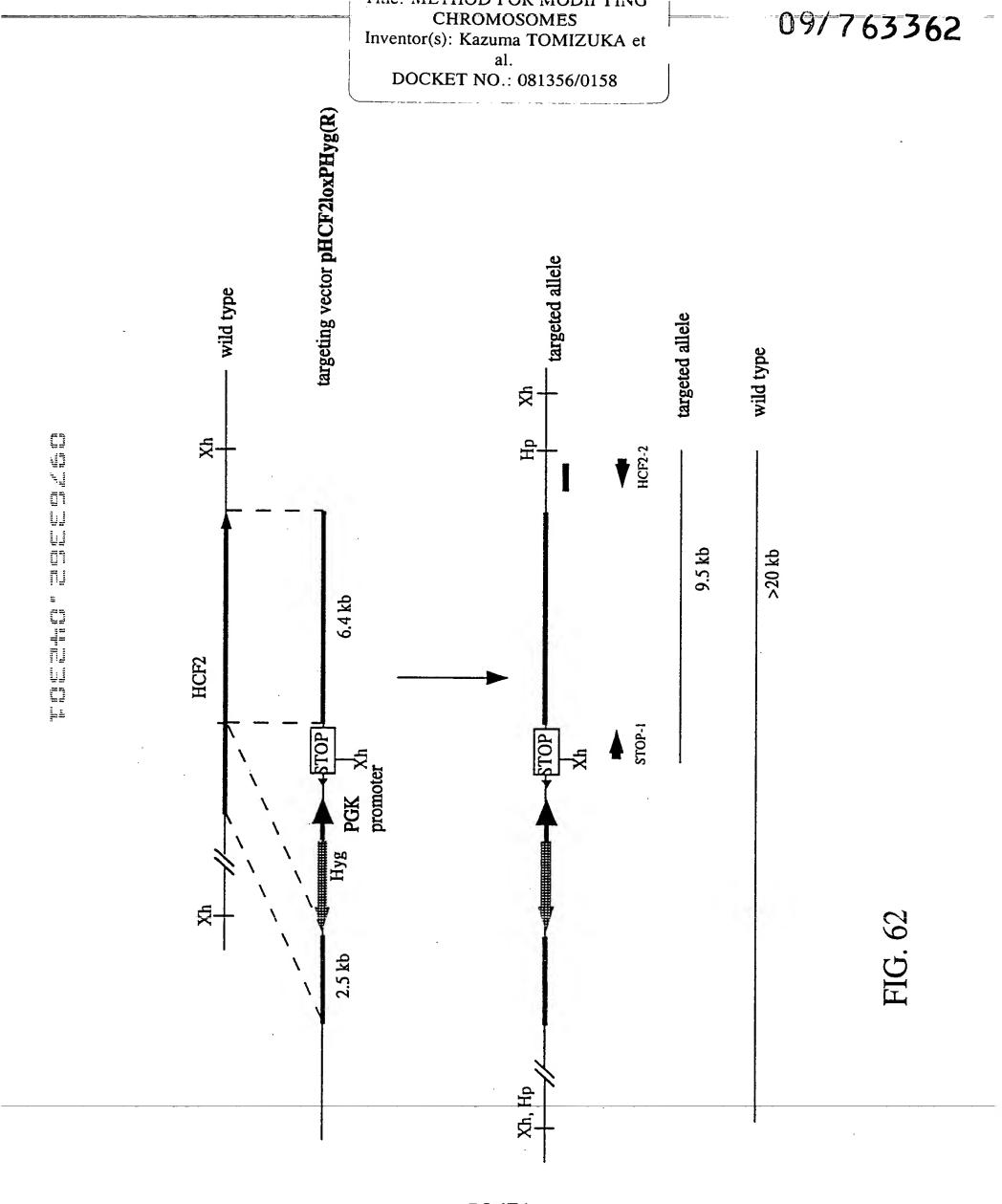
55/71

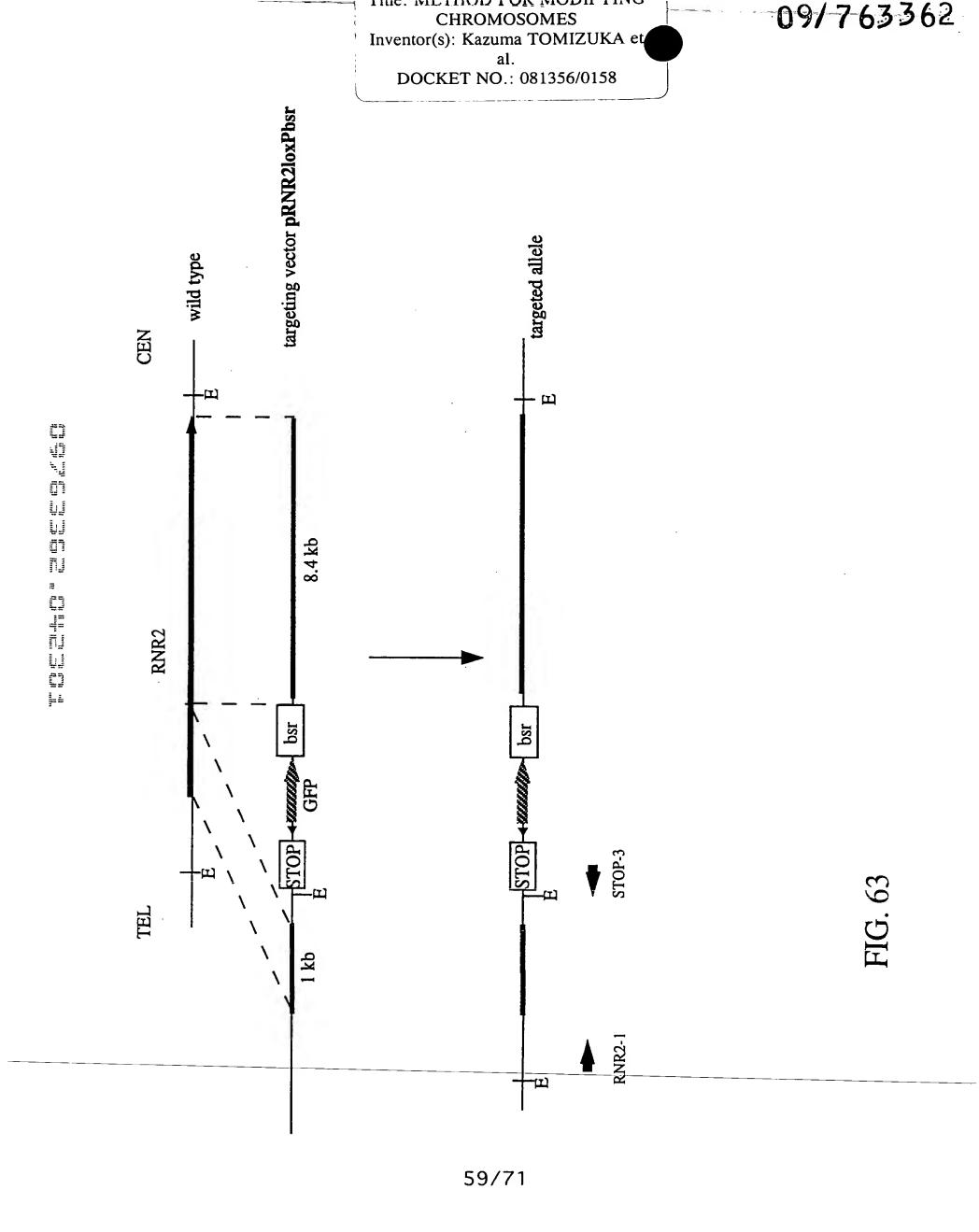
FIG. 60

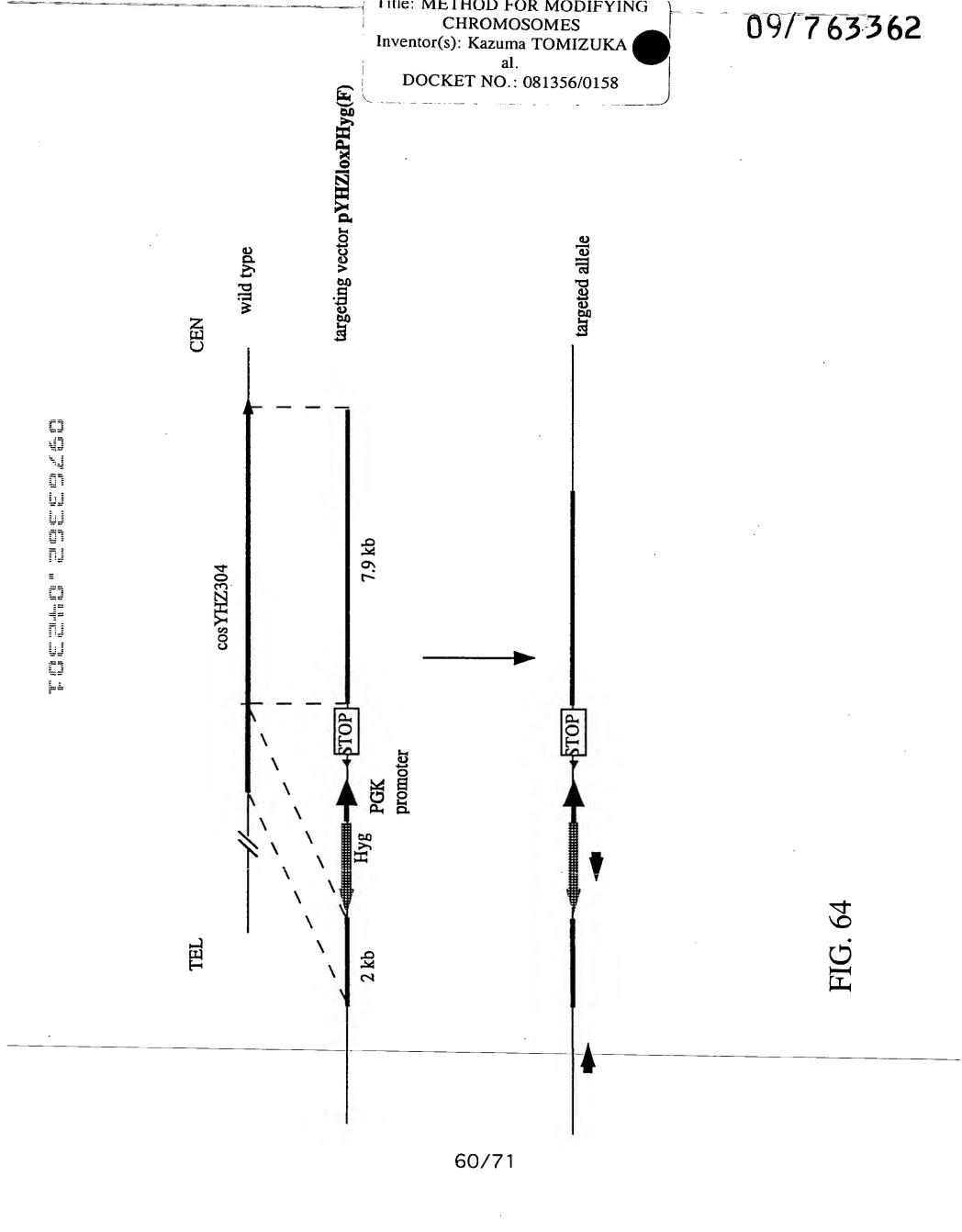






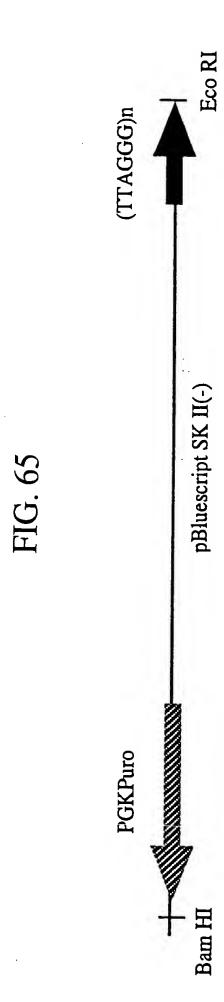


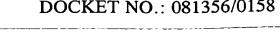


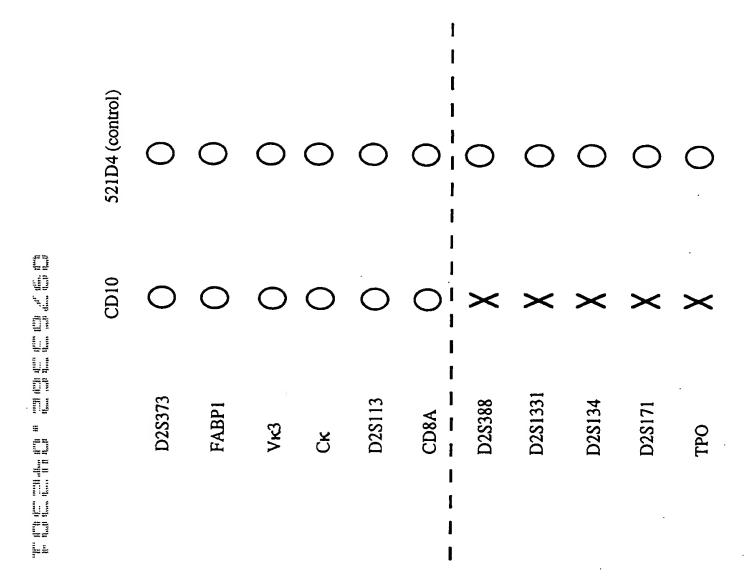


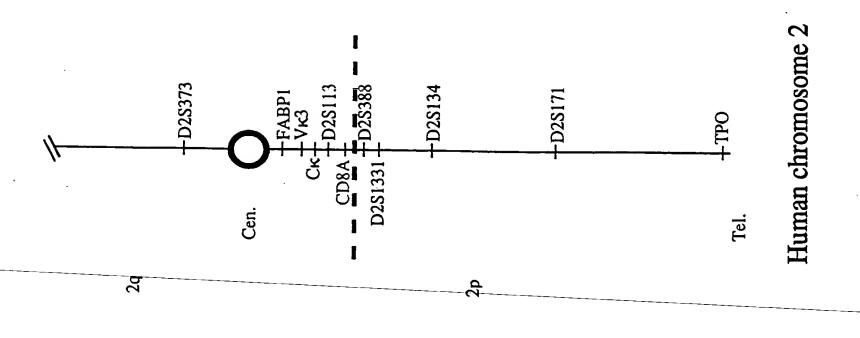
THE METHOD FOR MODIL CHROMOSOMES
Inventor(s): Kazuma TOMIZUKA et

al.



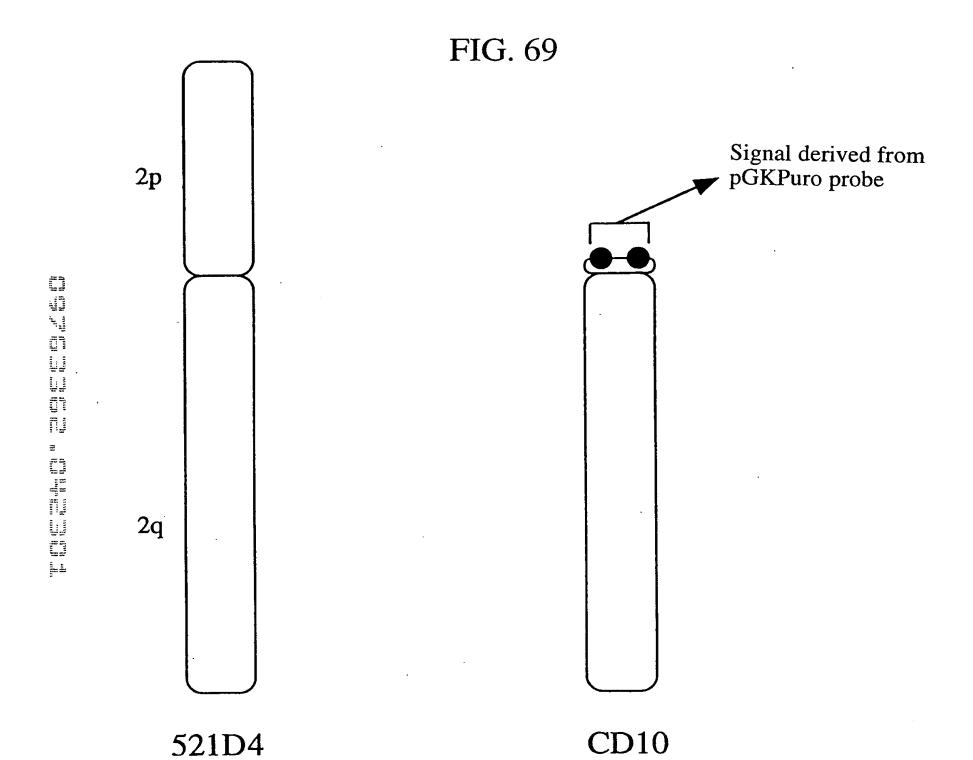


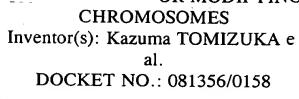


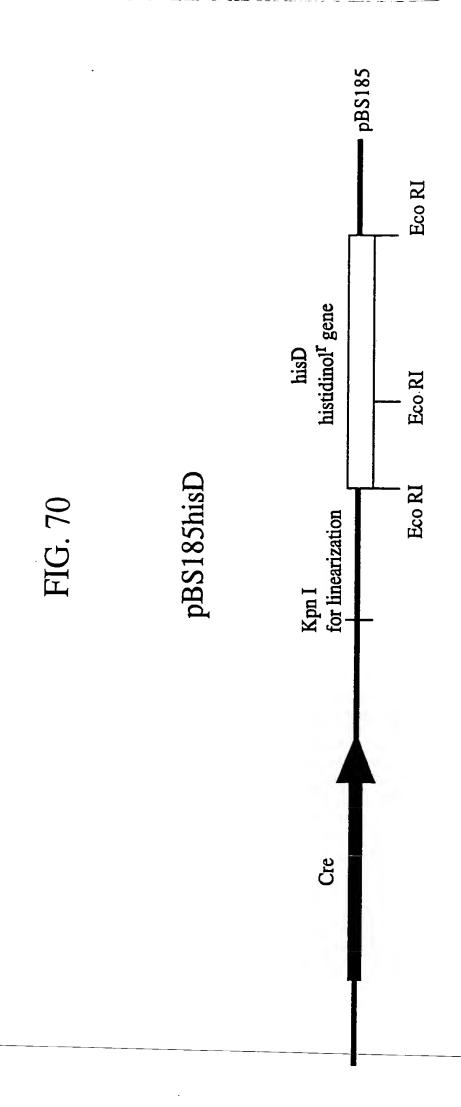


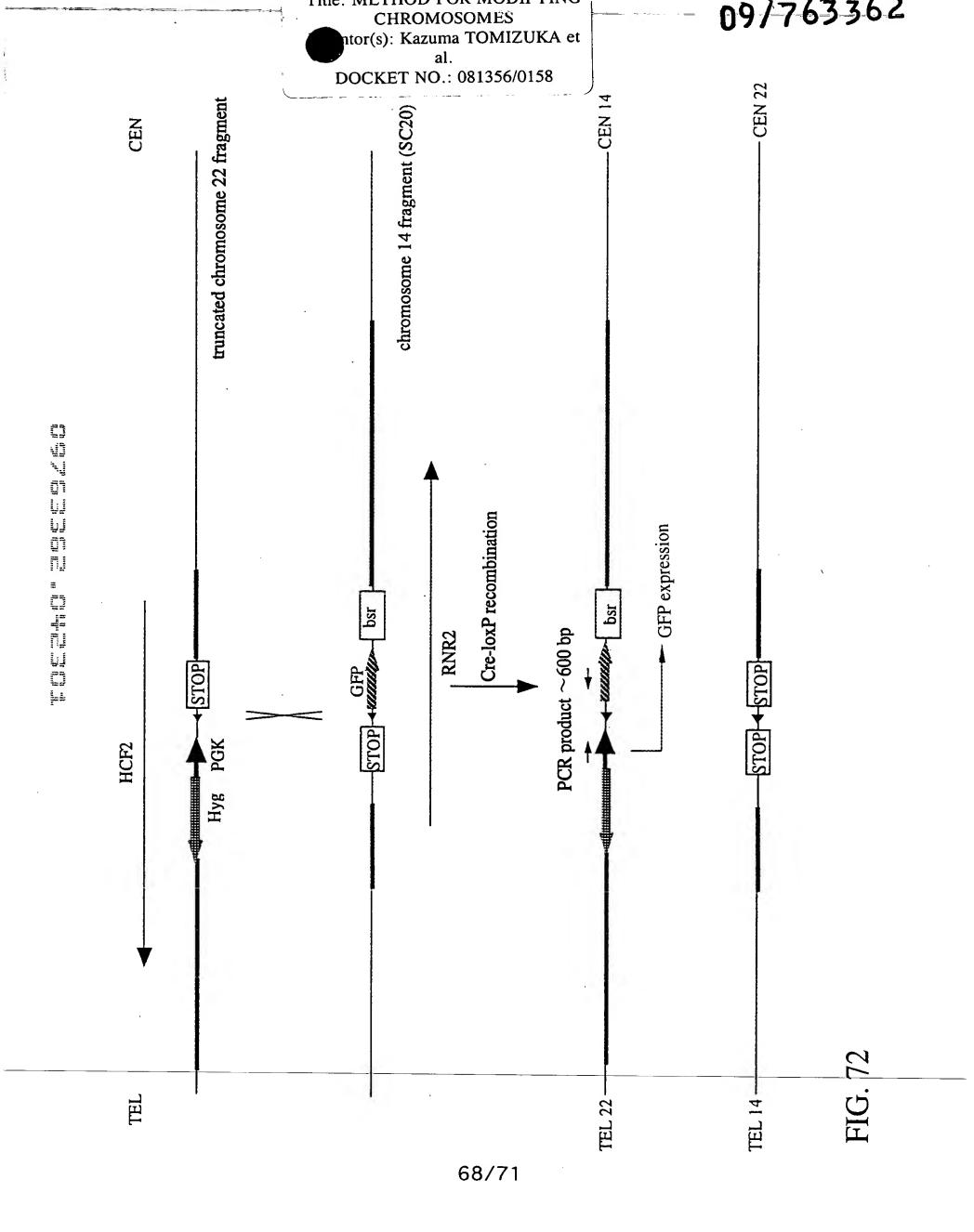
CHROMOSOMES

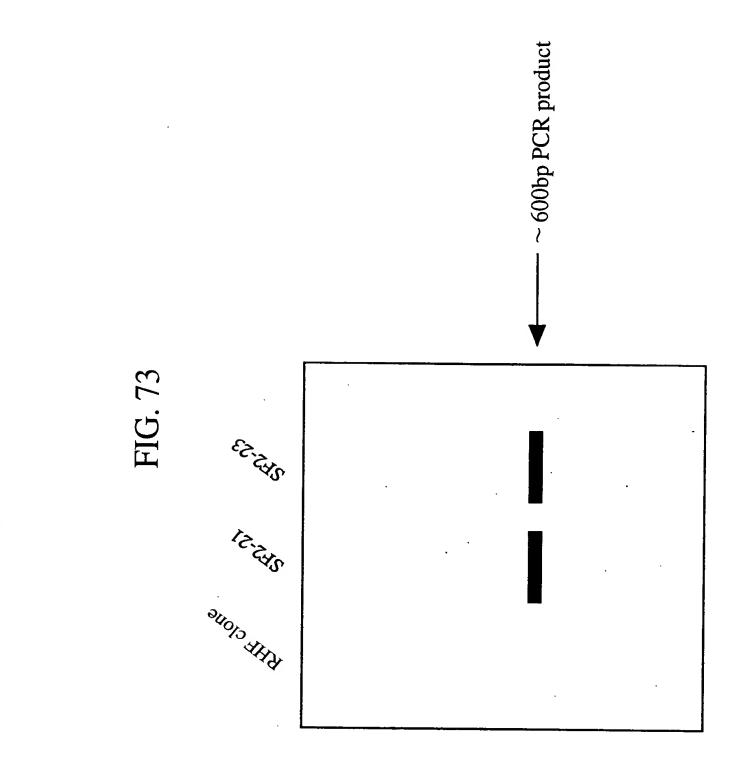
Inventor(s): Kazuma TOMIZUKA et











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(chromosome 22-specific probe)

FITC signal

(chromosome 14-specific probe) Rhodamine signal

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Rhodamine signal (pGKPuro probe)

(14qter-specific probe) FITC signal

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Title: METHOD FOR MODIFYING CHROMOSOMES ventor(s): Kazuma TOMIZUKA et

FIG. 75

